



NOTES

NEUROCUTANEOUS DISORDERS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Various disorders, primarily affecting skin, nervous system
 - Characterized by inherited/de novo tumor suppressor gene mutations → ↑ tumor formation incidence
- Tumor suppressor gene mutation → abnormal/absent protein → loss of control over important cell cycle regulators; cell growth, proliferation; intercellular communication → tumor formation

RISK FACTORS

- Parents with germline mutation

SIGNS & SYMPTOMS

- Various neurologic signs (lesion site-dependent)
- Eye, visual problems
- Mental, cognitive problems
- Skin lesions
- Benign, malignant nervous/other organ-system tumors

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI, CT scan

- See individual disorders

LAB RESULTS

- Genome testing

OTHER DIAGNOSTICS

- Eye examination

TREATMENT

SURGERY

- See individual disorders

OTHER INTERVENTIONS

- No current underlying mutation treatment
- Surveillance
- Symptom management

VISIT...

LANZAROTE
Caliente.COM

ATAXIA-TELANGIECTASIA

osms.it/ataxia-telangiectasia

PATHOLOGY & CAUSES

- Rare autosomal recessive disorder
 - Involves defective DNA repair
 - Characterized by progressive neurological abnormalities, most noticeably ataxia, oculocutaneous telangiectasias (superficial, dilated blood vessels of skin), immune deficiency, malignancy
- Mutation in ataxia-telangiectasia mutated (ATM) gene on chromosome 11; believed to be DNA surveillance (looks for damage → stops cell cycle to repair it/activates apoptosis)

Abnormal ATM protein

- Unable to phosphorylate
 - Tumor suppressor protein p53 → cell-cycle slowing/apoptosis absence → DNA repairing absence → mutation accumulation → malignant transformation → ↑ cell susceptibility to ionizing radiation
 - Tumor suppressor BRCA1 → ↑ breast cancer susceptibility
 - eIF-4E binding protein 1 controls protein synthesis when insulin present → probable cause of insulin resistance, disturbed growth
- Loses ribonucleotide reductase control → abnormal mitochondrial DNA synthesis, repair → probable cause of neurodegeneration, premature aging
- → chromosomal translocation, lymphocyte inversion → ↑ tendency of leukemias, lymphomas

Histology

- Central nervous system (CNS)
 - Brain atrophy, Purkinje cell loss in cerebellum (contributes to ataxia)
- Peripheral nervous system (PNS)
 - Malformed nuclei in Schwann cells

- Thymus hypoplastic
 - Fewer lymphocytes, Hassall's corpuscle absence

COMPLICATIONS

- Dysphagia → aspiration
- Pulmonary disease (chronic infection, restrictive interstitial lung disease)
- Malignancies
- Infection (due to T cell deficiency, inability to produce some antibodies, etc.)

SIGNS & SYMPTOMS

- Telangiectasias (blood vessel dilation in skin of face, neck, bulbar conjunctiva)
- Skin lesions (e.g. café au lait spots—flat, lightly-brown pigmented birthmarks)
- Immune deficiency in cellular, humoral immunity

Neurologic

- Abnormal gait, stance
- Ataxia (tremors, lack of voluntary coordinated movement)
- Dystonia (muscle contractions → repetitive movement/abnormal posture)
- Oculomotor apraxia (inability to coordinate head, eye movements)
- Nystagmus, acquired strabismus, reading problems
- Problems with speaking, chewing, swallowing can → aspiration
- Cognitive impairment

Pulmonary disease

- Respiratory muscles weakness
- Aspiration
- Interstitial lung disease

DIAGNOSIS

- Neurological symptom presence (e.g. progressive cerebellar ataxia)

LAB RESULTS

- Genetic testing
 - Mutation identification in both ATM gene copies
- Laboratory studies
 - ↑ alpha-fetoprotein in serum
 - ↓ ATM protein
 - ↓ immunoglobulins in serum (usually IgA, IgG)
 - Cell culture exposed to radiation (e.g. X-ray) → ↑ cell, chromosomal breakage

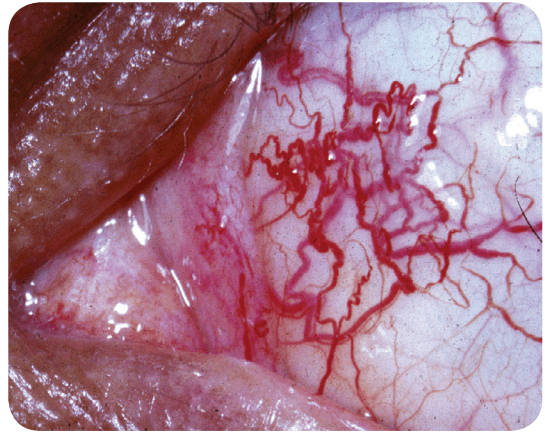


Figure 84.1 An ocular telangiectasia in an individual with ataxia telangiectasia.

TREATMENT

OTHER INTERVENTIONS

- Occupational, physical therapy (functional deficits)
- Monitor, treat main mortality causes
 - Infections, dysphagia, pulmonary disease, malignancy

NEUROFIBROMATOSIS TYPE I (NF1)

osms.it/neurofibromatosis-type-i

PATHOLOGY & CAUSES

- Rare autosomal dominant disorder
 - Characterized by ↑ tumor incidence
 - AKA von Recklinghausen disease, NFI
- Mutation in neurofibromin 1 gene (NF1) on chromosome 17 → abnormal/absent neurofibromin 1 protein (usually acts as tumor suppressor) → unable to control RAS pathway (stays trapped in active form) → loss of cell growth, division control

TYPES

- Small mutations in one NF1 gene copy → mild phenotypes

- Deletion of one NF1 gene → more severe phenotypes
- New mutation appearing in postzygotic stage → some cells have normal NF1 genes, some have mutations → segmental neurofibromatosis
- Both NF1 genes mutated → complete NF1 protein production loss

COMPLICATIONS

- Cognitive/learning disability, seizure, hypertension

SIGNS & SYMPTOMS

- $\geq$ six café au lait macules

Freckling

- Similar to café au lait macules but smaller, appearing later in groups with tendency for inguinal, axillary region

Lisch nodules (NF1-specific)

- Lifted tan-colored iris hamartomas

Neurofibromas

- Peripheral
 - Benign peripheral nerve sheath tumors; consist of many cells (primarily Schwann cells)
 - **Location:** skin, along nerve, nerve root next to spine
- Plexiform (leading morbidity cause)
 - Superficial, deep/mixed nerve overgrowth
 - Can compress adjacent structures (e.g. airways), invade surrounding tissue, become malignant
- Nodular
 - Superficial/deep hard lesions
 - Usually not invading tissue but can become malignant

Optic pathway glioma (OPG)

- Proptosis, visual problems

Malignant peripheral nerve sheath tumor (MPNST)

- Swelling in extremity; pain; numbness, burning sensation; extremity movement difficulty

Neurologic manifestations

- Speech, language delays; attention deficit hyperactivity disorder (ADHD)

Bone abnormalities

- Long bone dysplasia (anterolateral bowing)
 - Narrowed medullary canal, cortical thickening, pathologic fractures
- Pseudoarthrosis
 - Fake joint forming at previous fracture site
- Scoliosis; osteoporosis
- Short stature

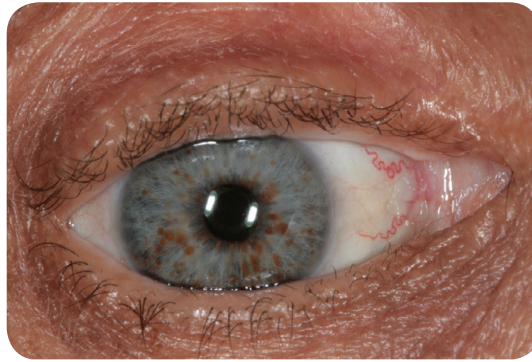


Figure 84.2 Lisch nodules in the iris of an individual with neurofibromatosis. Hamartomata of the iris constitute part of the diagnostic criteria for neurofibromatosis.

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Bright spots (areas of $\uparrow$ signals in T2 imaging)

Neuroimaging

- Megalencephaly ($\uparrow$ brain volume)

LAB RESULTS

- Genetic testing (diagnosis confirmation)

OTHER DIAGNOSTICS

- Clinically
 - Neurology, genetics, ophthalmology evaluation
 - Parent, sibling history, examination helpful
- At least two following features needed for diagnosis
 - $\geq$ six café au lait macules
 - $\geq$ two neurofibromas
 - Freckling
 - Optic glioma
 - $\geq$ two Lisch nodules
 - Characteristic bony lesion
 - First-degree relative diagnosed with NF1



Figure 84.3 Numerous cutaneous neurofibromata on the skin of an individual with type I neurofibromatosis.

TREATMENT

MEDICATIONS

Mass effect tumors

- Selumetinib
 - MEK 1/2 inhibitor; orphan drug for NF1

treatment → volume shrinkage

MPNSTs / OPGs

- Chemotherapy

Neurologic abnormalities

- Stimulants

SURGERY

Mass effect tumors

- Surgical removal

MPNSTs

- Surgical excision with radiation therapy

PSYCHOTHERAPY

Neurologic abnormalities

- Speech, occupational therapy

OTHER INTERVENTIONS

- Orthopedic interventions

Neurologic abnormalities

- Physical therapy

NEUROFIBROMATOSIS TYPE II (NF2)

osms.it/neurofibromatosis-type-ii

PATHOLOGY & CAUSES

- Uncommon autosomal dominant disorder
 - Characterized by ↑ neural tumor incidence (schwannomas, meningiomas)
- Mutations in neurofibromin 2 (NF2) gene on chromosome 22 → abnormal NF2 protein (i.e. merlin)
 - Cell membrane protein acts as tumor suppressor → loss of contact inhibition (likely) → ↑ tumor development risk
- Usually appears in young adulthood

TYPES

- Phenotype is mutation type-dependent
 - Nonsense, frameshift → severe phenotypes
 - Missense, inframe deletions → mild phenotypes

COMPLICATIONS

- Vestibular schwannoma
- Meningiomas (intracranial, spinal)
- Neuropathies (facial, polyneuropathy)
- Gliomas
- Eye lesions (e.g. cataracts, retinal hamartomas)

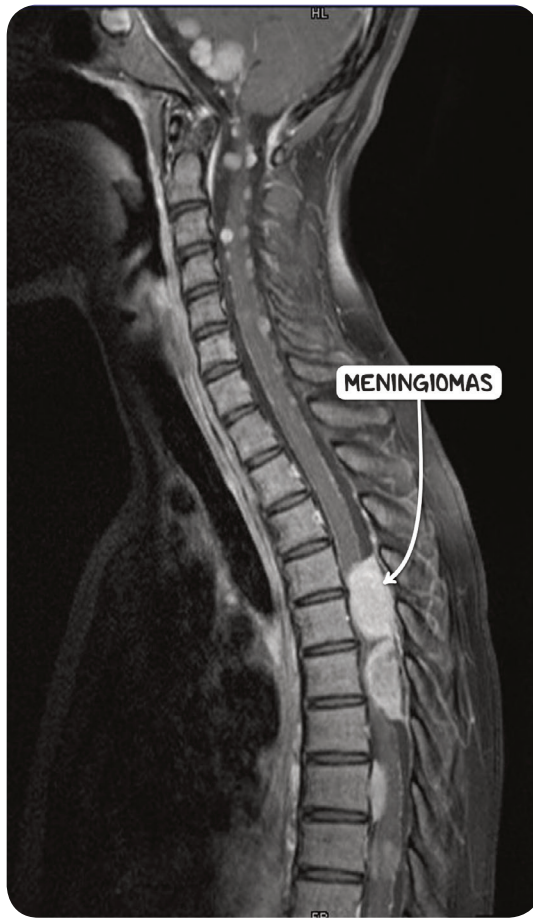


Figure 84.4 An MRI scan of the head in the axial plane demonstrating bilateral acoustic Schwannomas in an individual with type II neurofibromatosis.

SIGNS & SYMPTOMS

- Skin lesions (cutaneous, subcutaneous tumors)

Neurologic disorders

- Vestibular schwannomas (may be bilateral)
 - Progressive hearing loss, balance problems, tinnitus
- Meningiomas
 - Extremity weakness, double vision, incontinence, seizure
- Gliomas
 - Headache, vomiting, visual loss
- Spinal tumors
 - Muscle pain, weakness; paresthesias

- Other non-neoplastic lesions (e.g. meningioangiomatosis—benign leptomeninges lesions with good vascularization)
- Visual impairment

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Nervous system
 - For individuals with first-grade relatives diagnosed with NF2

LAB RESULTS

- Molecular testing for mutation
 - For individuals with first-grade relatives diagnosed with NF2

OTHER DIAGNOSTICS

- At least one of following needed
 - Bilateral vestibular schwannomas < 70 years old
 - Unilateral vestibular schwannoma < 70 years of age + first degree relative with NF2
 - Neurofibroma, meningioma, glioma, non-vestibular schwannoma, cataract or cerebral calcifications + first degree relative with NF2/unilateral vestibular schwannoma without schwannomatosis gene mutations
 - Multiple meningiomas + unilateral vestibular schwannoma/two of neurofibroma, glioma, cerebral calcification, cataract, non-vestibular schwannoma
 - NF2 gene mutation from blood/detecting same mutation in two different tumors
- Skin, eye examination
 - For individuals with first-grade relatives diagnosed with NF2

TREATMENT

MEDICATIONS

- Monoclonal antibodies against vascular endothelial growth factor (VEGF) → hearing improvement, tumor shrinkage

SURGERY

- Removal
 - Vestibular schwannomas; meningioma (surveillance until symptomatic)

OTHER INTERVENTIONS

- Stereotactic radiosurgery, radiotherapy
 - Vestibular schwannomas; meningioma (surveillance until symptomatic)



Figure 84.5 An MRI scan of the head in the axial plane demonstrating bilateral acoustic Schwannomas in an individual with type II neurofibromatosis.

NF1/NF2 OVERLAPPING CHARACTERISTICS SUMMARY

	NF1	NF2
CAFÉ AU LAIT MACULES	Common	Less common
LISCH NODULES	Present	Absent
SCHWANNOMAS UNDERGO MALIGNANT TRANSFORMATION	Yes	No
SPINAL ROOT TUMORS	Neurofibromas	Schwannomas
COGNITIVE IMPAIRMENT	Present	Absent
PREVALENCE OF BILATERAL ACOUSTIC SCHWANNOMAS	Low	High

STURGE–WEBER SYNDROME

osms.it/sturge-Weber-syndrome

PATHOLOGY & CAUSES

- Uncommon congenital disorder affecting blood vessels on face, brain, eyes
- **GNAQ gene mutation** → abnormal guanine nucleotide binding protein → loss of some intracellular signal pathway control → **capillary angiomas** development → hypoxia, venous stasis, thrombosis (probable tissue damage cause)
- Mutation occurrence
 - Early embryogenesis stages → probably affect more vascular cell precursors → Sturge–Weber syndrome (SWS)
 - Later embryogenesis stages → believed to affect endothelial cell precursors → nonsyndromic port wine stains (malformed facial capillaries)

COMPLICATIONS

- Intellectual disability
- Hydrocephalus (probably due to venous stasis, thrombosis)
- Glaucoma (↑ intraocular pressure)

SIGNS & SYMPTOMS

Port wine stain

- Newborns
 - Flat pink lesions
- Grows bulging out, turns to red wine color as individual ages
- Dilated blood vessels injury-prone → superficial bleeding → hypertrophy, nodularity
- Usually appears on forehead, upper eyelids

Leptomeningeal vascular malformation

- Big malformed intracerebral veins, usually drain in deep venous system
- Venous stasis → chronic ischemia → atrophied brain parenchyma, **calcific deposits**

Seizures (epilepsy)

- Affect young children
- Usually start as focal → become generalized

Hemiparesis

- Affects extremities contralateral to brain lesion
- ↓ motor function

Ophthalmologic problems

- Visual defects when brain's occipital region affected
- Choroid hemangiomas → ↑ intraocular pressure
- Episcleral, conjunctival hemangiomas

Endocrine problems

- Growth hormone deficiency
- Central hypothyroidism

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Contrast enhancement
- Presence, position, range of malformed capillaries, veins

CT scan

- Calcifications

OTHER DIAGNOSTICS

- Characteristic neurologic, ophthalmic, skin manifestations

TREATMENT

MEDICATIONS

- Antithrombotic therapy
- Topical medications
 - Managing intraocular pressure
- Anticonvulsants
 - Manage seizure

SURGERY

- Epileptogenic tissue removal
 - Manage seizure
- Hemispherectomy (disabling half of brain)
 - Manage seizure

OTHER INTERVENTIONS

- Photothermolysis (laser produced heat)
 - Skin lesions

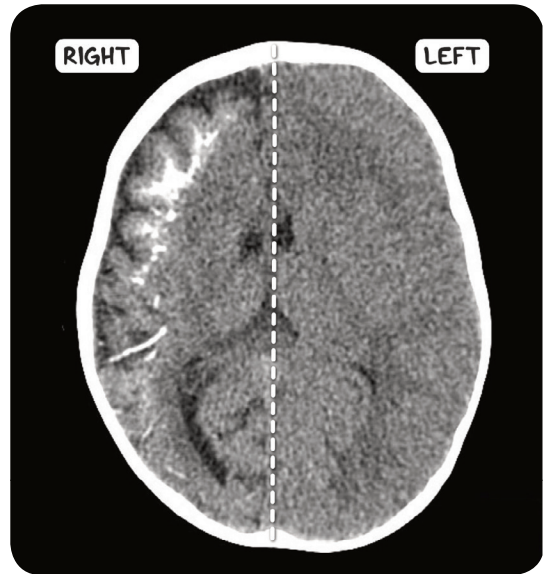


Figure 84.6 A CT scan of the head in the axial plane of an individual with Sturge-Weber syndrome. There is calcification and volume loss of the cerebral cortex on the right side.

TUBEROUS SCLEROSIS

osms.it/tuberous-sclerosis

PATHOLOGY & CAUSES

- Autosomal dominant disorder
 - Characterized by hamartoma, benign neoplasm development involving many organ systems
- Mutation in one/both genes
 - *TSC1* on chromosome 9 → abnormal/absent hamartin
 - *TSC2* on chromosome 16 (more commonly mutated) → abnormal/absent tuberlin
- Abnormal hamartin, tuberlin can not form/form inactive complex → control loss over kinase mechanistic target of rapamycin (mTOR)
 - Anabolic metabolism, cell size regulator → giant-cell tumors

- Mutation range-dependent
 - One copy mutated → cortical, subependymal tubers
 - Both copies mutated → subependymal giant-cell astrocytomas
- ↑ malignancy risk

COMPLICATIONS

- Seizure (leading morbidity cause)
- Autism spectrum disorders
- Intellectual disability
- Pneumonia
- Heart, renal failure

SIGNS & SYMPTOMS

Skin lesions

- Ash-leaf spots (hypomelanotic macules)
- Angiofibromas on cheeks
- Ungual fibromas (small tumors growing under nails)
- Shagreen patches (thick, pigmented, dimpled skin lesion usually on lower back)
- Characteristic brown plaques on infant forehead

Brain lesions

- Glioneuronal hamartomas, subependymal nodules
 - Seizure, intellectual disability
- Subependymal giant-cell tumors
 - Hydrocephalus → headaches, vomiting, visual problems, depression, appetite loss
- White matter lesions

Cardiovascular lesions

- Cardiac rhabdomyoma (benign heart tumor)
 - Blood flow obstruction, cardiac murmurs

Renal lesions (angiomyolipomas)

- Pain, irregular renal function

Pulmonary lesions

- Diffuse interstitial fibrosis/lymphangiomyomatosis (systemic disease → cystic lung destruction)
 - Dyspnea, pneumothorax

Ophthalmic lesions

- Retinal hamartomas (flat, translucent lesions); eyelid angiofibromas

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- With, without contrast enhancement
 - Cortical glial hamartomas
 - Subependymal nodules/giant-cell tumor
 - White matter lesions
 - Renal angiomyolipomas/cysts

LAB RESULTS

Genetic testing

- Mutation identification in *TSC1/TSC2* genes of healthy tissue cells
 - Can establish diagnosis without clinical manifestation
- Clinically uncertain diagnosis confirmation
- Prenatal diagnosis

OTHER DIAGNOSTICS

- Presents with at least two major symptoms
- Presents with one major, two/more minor symptoms
 - “Confetti” skin lesions (small hypomelanotic macules)
 - ≥ three dental enamel pits
 - ≥ two intraoral fibromas
 - Retinal achromic patch
 - Multiple renal cysts
 - Nonrenal hamartomas
- Full parental evaluation once child diagnosed
- Skin, neurologic, ophthalmic examination
- Vogt triad
 - Seizure, facial angiofibroma, intellectual disability



Figure 84.7 Numerous facial angiofibromas in an individual with tuberous sclerosis.

TREATMENT

MEDICATIONS

Seizure management, monitoring

- Infantile seizures: corticotropin (ACTH)/vigabatrin
- Partial seizures: many drugs (such as oxcarbazepine)
- Refractory epilepsy
 - Everolimus (mTOR inhibitor)

Tumor management

- Medical therapy (e.g. everolimus)

SURGERY

Seizure management, monitoring

- Refractory epilepsy
 - Epilepsy surgery

Tumor management

- Surgical removal if possible
- Angiomyolipoma embolization

Lungs

- Lung transplantation

PSYCHOTHERAPY

Cognitive, behavioral problems

- Special needs educational programs
- Occupational therapy
- Social support
- Psychiatric therapy

OTHER INTERVENTIONS

Seizure management, monitoring

- Refractory epilepsy
 - Ketogenic diet
 - Vagus nerve stimulation

Skin lesions

- Sun protection
- Laser therapy
- Dermabrasion (wearing away of skin)

Lungs

- Pleurodesis
 - Adhesion of two pleurae → pneumothorax prevention

VON HIPPEL–LINDAU DISEASE

osms.it/von-hippel-lindau

PATHOLOGY & CAUSES

- Autosomal dominant disorder
 - Characterized by formation of many different benign, malignant tumors (hemangioblastomas, renal cell carcinoma, pheochromocytoma)
- Mutation affects von Hippel–Lindau (VHL) tumor suppressor gene on chromosome 3 → abnormal VHL protein
 - Lost ability to deactivate hypoxia induced factor 1 alpha (HIF1A), 2 alpha (HIF2A) → HIF1A starts continuously producing erythropoietin while HIF2A produces VEGF → cellular metabolism,

growth dysregulation → highly vascular tumor formation

- Cilia centrosome, microtubules dysregulation → cyst formation in pancreas, liver, kidneys
- Dysregulation of extracellular matrix → malignant behavior
- Affected people usually have one inherited mutated allele but development requires other allele mutation/deletion/inactivation

TYPES

- Two types of VHL disease (based on pheochromocytoma development risk)

Type 1

- ↓ risk
- Usually associated with large deletions, frameshift, nonsense mutations

Type 2

- ↑ risk
- Usually associated with missense mutations

SIGNS & SYMPTOMS

Hemangioblastomas

- Usually affect cerebellum, spinal cord, retina
 - Benign, well defined tumors
 - Highly vascular
 - Can pressure adjacent structures/bleed

Retinal capillary hemangioblastomas

- Visual loss
- Retinal detachment
- Glaucoma

Renal cell carcinomas (RCC)

- Haematuria
- Flank pain (between ribs, hips)
- Abdominal mass

Pheochromocytomas

- Headaches
- High blood pressure, ↑ heart rate
- Skin sensations

Pancreatic tumors

- Usually asymptomatic
 - Epigastric pain
 - Diarrhea

Endolymphatic sac tumors of middle ear (ELSTs)

- Hearing loss
- Tinnitus
- Vertigo

DIAGNOSIS

DIAGNOSTIC IMAGING**CT scan**

- Tumor visualization
- ELSTs
 - Retrolabyrinthine calcifications

MRI

- Tumor visualization
- ELSTs
 - Hyperintense T1, heterogeneous T2 focal signals

LAB RESULTS

- Pheochromocytomas
 - **Serum testing:** ↑ normetanephrine to metanephrine ratio
- Genome testing
 - Southern blotting
 - Genome sequencing
- Prenatal diagnosis
 - Amniocentesis
 - Chorionic villus sampling

OTHER DIAGNOSTICS

- Retinal examination
- ELSTs
 - Auditory tests
- Genetic counseling

TREATMENT

MEDICATIONS

- Pheochromocytomas
 - Alpha-adrenergic blockade

SURGERY

- CNS hemangioblastomas, pancreatic tumors, ELSTs
 - Removal (when symptomatic)
 - Cochlear implants: individuals with hearing loss

- RCC
 - Partial nephrectomy
- Pheochromocytomas
 - Removal

OTHER INTERVENTIONS

- CNS hemangioblastomas, pancreatic tumors, ELSTs
 - Stereotactic radiosurgery, radiation therapy

- Retinal capillary hemangioblastomas
 - Laser photocoagulation
 - Cryotherapy
- RCC
 - Cryotherapy
 - Radiofrequency ablation
- Pheochromocytomas
 - Catecholamines production surveillance